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Natural Approaches to Treating Addiction

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Introduction

Addiction is a worldwide problem resulting in great economic, health, and social burdens. It is estimated that 4.7% of the global population ages 15–64, or 184 million people, consume illicit drugs annually.¹

Addiction to legal substances is also a problem. According to the Centers for Disease Control and Prevention (CDC), 20.8% of all adults smoke cigarettes, totaling 45.3 million people,² and smoking remains the leading preventable cause of death in the United States.³ The National Epidemiological Survey on Alcohol and Related Conditions indicates that the prevalence of lifetime alcohol abuse is 17.8%, and the prevalence of lifetime alcohol dependence is 12.5% in the United States.⁴

Addiction is a chronic condition in which there is an obsession and compulsion to seek and use a substance (or engage in a behavior) that induces a pleasant state or relieves distress. Continued use of the addictive substance (or engaging in the addictive behavior) induces adaptive changes in the brain that lead to tolerance, physical dependence, uncontrollable craving, and a characteristic set of signs and symptoms upon withdrawal.

Common addictive substances include alcohol, nicotine, barbiturates, benzodiazepines, opioids, and stimulants. Behavioral addictions, also known as process addictions, such as gambling, eating disorders, and sex, have also recently been included in the scope of true addiction as they have the same core components as substance abuse, including mood modification, tolerance, withdrawal, and relapse.

In both substance and behavioral addictions, the body becomes “addicted” to the neurochemical modifications caused by the substance or experience even more than to the substance itself. There is also a strong neurobiologic link between behav-

ioral addictions and substance-abuse disorders, given the substantial co-occurrence of such conditions.

There is a great deal of research on the various forms of addiction and the role that neurotransmitters and hormones play in the initiation, progression, and relapse of these disorders. In addition, there are numerous studies attempting to elucidate specific genetic and environmental risk factors for addiction.

The basic physiology of the various addictions involves similar mechanisms. First, the mesolimbic dopamine reward pathway can be physically altered by an addictive substance, resulting in uncontrolled cravings. In addition, the decision-making prefrontal cortex, which suppresses inappropriate reward response, can become altered. Thus, despite severe consequences, accelerated “go” signals and impaired “stop” signals result in uncontrolled use. In addition, genetic defects in reward pathway neurotransmission and stress-related developmental brain abnormalities can predispose patients to addiction.⁵

Risk Factors for Addiction

Assessing risk factors for addiction is complex because both genetics and environment play roles. There appears to be an interplay between functional alleles influencing pharmacodynamic (tissue response), pharmacokinetic (absorption, distribution, and metabolism), and environmental factors, such as early life stress, underage drug exposure, and availability of addictive agents.⁶ Studies indicate that one of the strongest associations for risk of addiction is depression.^{7,8} In addition, severe childhood stressors have been associated with increased vulnerability to addiction.⁹

For alcohol dependence, research has shown an increased prevalence in men, whites, Native Americans, younger and unmarried adults, and people with lower incomes than most

people. There is also a strong correlation between mood, anxiety, personality disorders, other substance-use disorders and alcohol-use disorders.⁴ One prospective study examined risk factors for alcohol-use disorders in early and middle adulthood by assessing characteristics of study participants at age 18. The results showed that parental drinking, risk taking, and use of cigarettes and marijuana predicted heavy drinking at age 35, while planning to attend college predicted more heavy drinking at age 22 and less-frequent heavy drinking at age 35.¹⁰

Genetics and Addiction

Family, adoption, and twin studies indicate a genetic basis for addiction. Evidence from twin studies has shown that there is a moderate-to-high genetic influence on addiction with heritability estimates ranging from 0.30 to 0.70.¹¹ Twin and family studies have indicated substantial genetic contributions to smoking behaviors. Research suggests that genetically slow metabolism of nicotine is associated with a lower level of dependence. Nicotine dependence appears to be influenced by genes coding for some nicotine receptor subtypes, some neurotransmitter genes, and genes involved in neural connectivity.¹²

A large twin study evaluated genetic and environmental influences to the initiation of use and progression to more serious use of alcohol, cigarettes, and marijuana during adolescence. The study results showed that common environmental influences that make twins more similar tended to be greater for initiation, while genetic influences were stronger for heavier use.¹³

Much research has attempted to identify specific gene variants as risk factors for addiction. Research has shown that individuals carrying one or two copies of the 118G mu-opioid receptor variant allele may have increased risk for opiate and alcohol addictions,¹⁴ and patients with this polymorphism have significantly lower relapse rates to alcoholism when treated with naltrexone.¹⁵

In another study, a variant in the nicotinic acetylcholine receptor gene cluster on chromosome 15q24 was associated with smoking quantity, nicotine dependence, and the risk of lung cancer and peripheral artery disease (PAD) in populations of European descent.¹⁶ Other research has shown that a genetic variant in the aldehyde dehydrogenase 2 gene is associated with drinking behavior and reduced risk of developing alcohol dependence.¹⁷

Neurotransmitters and Hormones in Addiction

Dopamine

Dopamine is a neurotransmitter that acts on five receptors, primarily in the substantia nigra and the ventral tegmental areas in the brain. Dopamine plays a significant role in behavior and cognition, mood, motivation and reward, and sleep, among other functions. The role dopamine plays in motivation and reward makes this agent an obvious area of research for examining addictive behavior.

Many drugs that are abused, including alcohol, nicotine, and stimulants, produce their effects by stimulating the mesocorticolimbic dopaminergic system.¹⁸ This also explains, at least in part, the overlap between addictions such as alcohol and nicotine.¹⁹ Research has shown that the reinforcing effects of drugs are associated with large and fast increases in extracellular dopamine, which is similar to physiologic dopamine cell firing but is more intense. Dopamine cells fire in response to salient stimuli. Thus, this intense firing with drug use is experienced as highly salient, which drives motivation, learning, and attention.

Imaging studies have shown that repeated drug use raises the threshold needed for cell firing and leads to marked decreases in dopamine release and dopamine D2 receptors. This decrease in

Research has linked abnormal circadian rhythms with addiction.

dopamine activity is associated with reduced regional activity in the orbitofrontal cortex (resulting in compulsive behaviors), the cingulate gyrus (resulting in impulsivity), and the dorsolateral prefrontal cortex (resulting in impaired regulation of intentional actions).²⁰ In addition, research has linked abnormal circadian rhythms with addiction, which is believed to be mediated through the mesolimbic dopaminergic system.²¹

Serotonin

Serotonin is an important neurotransmitter for regulating mood, aggression, appetite, and sleep. Several pharmaceuticals, such as those used to treat depression and anxiety, are aimed at modulating serotonin metabolism. Researchers have shown decreased levels of platelet serotonin in subjects who were addicted to alcohol.²² In addition, animal models have shown that nicotine administration increases serotonin turnover,²³ and cessation of repeated nicotine administration results in increased sensitivity to serotonin receptors and decreased serotonin turnover. This may be related to the manifestation of nicotine-withdrawal symptoms.²⁴

Gamma-Aminobutyric Acid

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter and is synthesized from glutamate. Agents that act as GABA agonists generally function as anxiolytics. Several substances, such as alcohol, anesthetics, and benzodiazepines modulate GABA receptors. GABA(A) receptors have been implicated in the acute and chronic effects of alcohol addiction, including tolerance, dependence, and withdrawal.

Research has shown that GABA(A) receptors modulate anxiety and the stress response, which plays an important role in sustained drinking and relapse. In addition, the GABA(A) receptor subunit genes clustered on chromosome 4 are highly expressed in the reward pathway, and many studies have shown that one of these genes, GABRA2, is associated with alcoholism in humans.²⁵

Melatonin

Melatonin is a hormone secreted primarily from the pineal gland. This hormone functions as a potent antioxidant and regulates circadian cycles. Melatonin is synthesized from serotonin, thus making changes in serotonin levels relevant to melatonin production. In addition, melatonin appears to increase the binding of GABA to its receptors.

Research has shown that melatonin inhibits nicotine-stimulated dopamine release in certain cell types.²⁶ Although one study has reported elevated melatonin levels in smokers compared with nonsmokers,²⁷ more-recent research indicates that smoking significantly decreased melatonin content of the blood compared with the content of this hormone in nonsmokers.²⁸

Hypothalamic–Pituitary–Adrenal Axis

The stress response through the hypothalamic–pituitary–adrenal (HPA) axis is another area that plays a role in addiction. Stress is a significant risk factor for the development of addictions, and examining how the HPA axis functions with addiction is one area in which the interaction between genes and environment is apparent.

Both animal and human studies have demonstrated that the effects of stress on alcohol intake are mediated by core HPA axis genes and are associated with genetic variations in those genes.²⁹ Acute intake of alcohol and nicotine induces stress-like cortisol responses, and persistent use may alter HPA functioning.

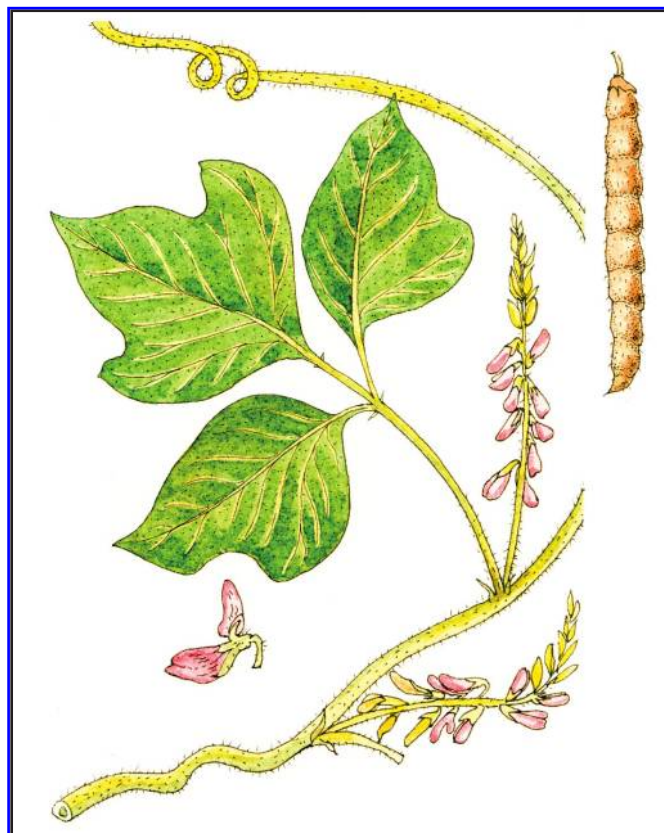
In addition, the risk for dependence and relapse may be associated with deficient cortisol reactivity to stress. Animal models have shown that there is an increase in relapse of drug-seeking behavior in highly stress-reactive mice.³⁰ The HPA axis is regulated by metabolic signals as well as through the limbic system and prefrontal cortex. Chronic and heavy intake of nicotine and alcohol may modify frontal–limbic interactions, which may account for changes in HPA responses seen in people who abuse alcohol and in smokers. In addition, addiction-proneness may be a result of a preexisting alteration in frontal–limbic interactions with the HPA axis, as shown in studies of the offspring of alcohol- and drug-abusing parents.³¹

Natural Therapies for Treating Substance Abuse

Kudzu

Pueraria lobata (kudzu), an edible vine used widely in Chinese medicine, has decreased alcohol consumption and limited alcohol withdrawal symptoms in studies. Puerarin, daidzin, and daidzein are three isoflavonoid constituents that are believed to give this plant many of its medicinal properties.

Several studies using alcohol-preferring rats have shown that kudzu root decreases alcohol consumption and the development of alcohol withdrawal symptoms, such as hypersensitivity, poor coordination, and tremors.^{32,33} Another interesting study found that daidzin works preventively as well.³⁴ The isoflavone puerarin has also been shown to counteract anxiogenic effects associated with withdrawal from chronic alcohol intake, and research suggests that this plant is a weak benzodiazepine site antagonist.³⁵



Pueraria lobata (kudzu).

Additional research also suggests that kudzu may affect norepinephrine and dopamine levels in the hippocampus and striatum.³⁶ Another study showed that puerarin from kudzu root combined with either antioxidant polyenylphosphatidylcholine from soy or curcumin from *Curcuma* spp. (turmeric) suppressed both the addiction-related and inflammation-related abnormalities of alcohol drinking.³⁷

In a clinical study, “heavy” alcohol drinkers were treated with either placebo or a kudzu extract for 7 days and then given an opportunity to drink their preferred brands of beer while in a naturalistic laboratory setting. The results showed that kudzu supplementation resulted in a significant reduction in the number of beers consumed, an increase in the number of sips and the time to consume each beer, and a decrease in the volume of each sip.³⁸ Studies also support the use of NPI-028, a Chinese herbal medicine composed of seven plants, including a significant concentration of puerarin from kudzu.³⁹

St. John's Wort

Hypericum perforatum (St. John's wort) modulates several neurochemical pathways; this is the proposed mechanism for the herb's effects on depression, alcohol withdrawal, and smoking cessation. Hypericin and hyperforin are believed to be the active constituents in this medicinal plant. Depression and alcoholism have some neurochemical similarities, such as low brain serotonin activities.

St. John's wort extract was compared with tricyclic and selective serotonin reuptake inhibitor (SSRI)-type antidepressants



Hypericum perforatum (St. John's wort).

to evaluate the uptake of serotonin and norepinephrine in rat brain slices. A dose-dependent inhibition was seen with serotonin and norepinephrine uptake comparable with that of

*More than 64% of subjects taking
St. John's wort in a study quit
smoking on a designated quit date.*

imipramine, desipramine, or fluvoxamine for serotonin, and a lesser effect for norepinephrine. These effects were not achieved with either hypericin or hyperforin alone.⁴⁰

Researchers have demonstrated that hyperforin enhances the extracellular levels of dopamine, noradrenaline, and serotonin, as well as the excitatory amino acid glutamate in the locus coeruleus.⁴¹ In studies with rats, *Hypericum* extract has been shown to enhance serotonin, norepinephrine, and dopamine levels⁴²; decrease symptoms of alcohol withdrawal⁴³; and reduce ethanol consumption.^{44–47}

H. perforatum has also been evaluated for smoking cessation because the relationship between smoking and depression is becoming apparent. Studies in mice have shown improvement in serotonin levels⁴⁸ and reduction in symptoms of nicotine withdrawal.⁴⁹ In a small human study, subjects who smoked more than 10 cigarettes per day were given St. John's wort for 1 week prior to a designated quit date. More than 64% of the subjects quit on the designated quit date, and 37.5% of those subjects had maintained smoking cessation at the 12-week follow-up.⁵⁰

Iboga

Tabernanthe iboga (iboga), a rainforest shrub native to equatorial Africa, has been used to treat stimulant addiction. *T. iboga* contains an indole alkaloid, ibogaine, which is derived from the bark of the root. Ibogaine is metabolized rapidly in the body to noribogaine. Animal studies have shown positive effects of ibogaine with regard to use of nicotine,⁵¹ alcohol,⁵² morphine, and cocaine.⁵³



Passiflora incarnata Linnaeus (passionflower or passiflora).

Ibogaine and noribogaine have both produced numerous neurologic effects as well. Ibogaine binds to serotonin uptake sites, kappa opioid receptors, N-methyl-D-aspartate (NMDA) receptors, and nicotinic receptors. Researchers suggest that kappa agonist and NMDA antagonist actions contribute to ibogaine's effects on opioid and stimulant self-administration. The binding of serotonin uptake sites may be responsible for ibogaine-induced decreases in alcohol intake, and the nicotinic receptor activity may mediate ibogaine-induced reduction of nicotine preferences.⁵³

Several studies have found that 18-methoxycoronaridine, a novel iboga alkaloid congener, appears to have substantial potential for broad use as an antiaddictive therapy without the neurotoxic effects seen with ibogaine.^{54,55}

Asian Ginseng

Panax ginseng (Asian ginseng) is a commonly used adaptogenic herb in Traditional Chinese Medicine. Various studies have demonstrated that ginseng saponins prevent behavioral hyperactivity induced by psychomotor stimulants.^{56,57}

Other Treatment Considerations

Velvet Bean

Although direct evidence is lacking using *Mucuna pruriens* (velvet bean, cowitch, cowhage, etc.) to treat addiction, the seed of this plant has been shown to contain a significant level of levodopa (L-dopa), the precursor to dopamine. Studies with a Parkinson-model in rats have shown that *M. pruriens* cotyledon powder supplementation significantly restored the endogenous levodopa, dopamine, norepinephrine, and serotonin content in the substantia nigra.⁵⁸ Thus, it is possible that *M. pruriens* may enhance moderate neurotransmitter levels in substance withdrawal.

Melatonin

As smoking has been shown to decrease melatonin levels, restoring melatonin levels may provide benefit for patients who

smoke. Research has shown that melatonin supplementation reduced nicotine-induced oxidative stress and morphologic changes in the lungs and livers of rats, suggesting that melatonin may be useful for combating free radical-induced oxidative stress and tissue injury that result from nicotine toxicity.⁵⁹ In addition, human studies have shown that an 0.3-mg dose of melatonin decreased nicotine-withdrawal symptoms.⁶⁰

Korean Angelica

One study showed that inhalation of the essential oil from *Angelica gigas* Nakai (Korean Angelica) significantly decreased both dopamine release in the nucleus accumbens and loco-

Human studies have shown that an 0.3-mg dose of melatonin decreased nicotine-withdrawal symptoms.

motor activity induced by a nicotine challenge in rats. The researchers concluded that the essential oils from *A. gigas* Nakai inhibit nicotine-induced behavioral and neurochemical sensitization, and these researchers suggest that this plant may be effective for treating nicotine addiction by modulating dopamine release in the nucleus accumbens.⁶¹

Passionflower

Passiflora incarnata Linnaeus (passionflower or passiflora) contains a benzoflavone moiety that is believed to be responsible for many of the biologic activities of this plant. The benzoflavone moiety has produced positive results in the reversal of, tolerance of, and dependence on, several addictive psychotropic drugs, such as morphine, nicotine, and alcohol in animal models.⁶² One study showed that the benzoflavone constituent prevented the expression of withdrawal effects significantly in alcohol-addicted mice with a significant decrease in anxiety behavior.⁶³

Kava

Kavapyrones, constituents of *Piper methysticum* (kava), have been shown to bind sites in the brain that are associated with addiction and craving. A pilot study found that kava may reduce the craving associated with addictions to such substances as alcohol, tobacco, cocaine, and heroin. The subjects reported a reduction in their desire for their drugs of choice. In addition, supplementation with a standardized amount of kavapyrones led to an apparent difference in abstinence between the experimental and placebo groups for alcohol intake.⁶⁴

5-Hydroxytryptophan

There is no direct evidence supporting the use of 5-hydroxytryptophan (5-HTP) with addiction. However, 5-HTP is the precursor to serotonin and can increase synthesis of serotonin in the central nervous system (CNS), and thus may be beneficial for serotonin support.

Gamma-Aminobutyric Acid

Currently, there are no studies supporting the use of gamma-aminobutyric acid (GABA) for treating addiction. GABA is the primary inhibitory neurotransmitter in the CNS and is used in complementary medicine for reducing anxiety and improving mood.

Acupuncture

Some reports have suggested that acupuncture application increases the levels of endorphins, enkephalin, epinephrine, norepinephrine, serotonin, and dopamine in the CNS and plasma.⁶⁵ Although there is conflicting evidence, some studies have shown efficacy using acupuncture for smoking cessation.⁶⁶

Conclusion

Addiction is a significant problem that requires much attention. Current research is evaluating the complex interplay between genes and environment to assess the risk of developing addictions. Researchers are also finding that changes in neurotransmitters and hormones play significant roles. Preliminary research with several natural therapies has shown promise in providing potential treatment options for various types of addiction. ■

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